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Date June 3, 2003

To Patrick Lewis, Ph.D.
Examiner
Art Unit 1623
United States Patent and Trademark Office
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Facsimile number 12372-00200001 / 703-308-4556

From John T. Kendall, Ph.D.
Technology Specialist

Re: SUSTAINED RELEASE DRUG COMPOSITIONS

Applicant:	Aki Kitagawa et al.
Application No.:	09/834,103
Filing Date:	April 12, 2001
Country:	United States
Our Ref.:	12372-002001

Number of pages including this page 4

Message **FOR THE ATTENTION OF PATRICK LEWIS, PH.D.**

At your convenience, kindly acknowledge receipt of this transmission by facsimile or telephone (617-521-7032).

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June 3, 2003

Patrick Lewis, Ph.D.
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Re: SUSTAINED RELEASE DRUG COMPOSITIONS

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Application No.:	09/834,103
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Dear Dr. Lewis:

I am writing to request a telephone interview to discuss the final Office Action dated January 8, 2003 (the "final action") issued in the above-referenced case. As you will recall, the previous, nonfinal Office Action dated July 25, 2002 included a rejection of claims 12-26 under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al, EP 0 913 149 A1 (Suzuki) in view of Igari et al., U.S. 5,344,644 (Igari). This rejection was maintained in the final action.

We do not agree with the rejection. However, in order to expedite prosecution, we propose the following amendment to independent claim 12 for your consideration. Also included is a summary of the issues that we wish to discuss during the interview.

Proposed Amendment (the added text is underlined and the deleted text is bracketed):

12. (Proposed Amendment) A method of producing a sustained release drug composition, the method comprising

providing a precipitating solution containing a mucopolysaccharide, a carrier protein, and a protein drug;

lowering the pH of the precipitating solution to a level sufficient to form an insoluble product comprising the mucopolysaccharide, the carrier protein, and the protein drug; and

collecting from the precipitating solution the insoluble product[.];

wherein, when prepared as an aqueous suspension, the protein drug contained in the product is released as an active form in a sustained release manner.

Support for the above amendments can be found throughout the Specification, e.g., at page 3, lines 9-15; page 4, lines 3-5; and page 10, lines 5-16 and in claims 12, 19, and 20 as originally filed.

Claim 12 as amended and its dependents are directed to a method of producing a sustained release drug composition in which the drug is a protein drug. Briefly, the compositions are precipitated by lowering the pH of a precipitating solution containing the protein drug, a mucopolysaccharide and carrier protein. Our specification specifically teaches that the pH is lowered to about 3 using aqueous hydrochloric acid (see, e.g., Examples 2 and 3, page 7, line 16 through page 8, line 15 and Examples 9 and 10, page 10 line 5 through page 11 line 6).

The compositions obtained by the claimed method exhibit sustained protein drug release rates that are unexpectedly superior to those of known sustained release drug compositions (see, e.g., Examples 2 and 3). Further, these compositions release the protein drug in active form (see, e.g., Examples 9 and 10). In other words, the protein drug that is released from the drug composition precipitated at pH 3 is not structurally or functionally compromised.

Suzuki discloses adjusting the pH of preparatory solutions with very dilute acetic acid (e.g., 1% aqueous solutions, Suzuki, page 5, lines 25-26) to dissolve certain ingredient (a) components. Igari describes the preparation of active peptide drug compositions at pH 4-8, preferably 5-8 (Igari, column 6, line 50-52). The recitation of the preferred pH range in Igari is prefaced with the following caveat:

> The pH of a solution prepared from the water-soluble composition of the present invention should be such that said pH will not exert any adverse influence upon the activity of the pharmacologically active peptide...(Igari, column 6, lines 43-46).

One of skill in the art would recognize that a pharmacologically active peptide can e.g., denature at acidic pH and would understand this statement to mean that when preparing a active peptide drug compositions, a pH of 4 or above should be employed. Clearly, the art of record does not suggest that sustained release protein drug compositions could be advantageously produced at a pH less than 4. Thus at the time our invention was made, it would not have been expected that a protein drug would be successfully reproduced and sustained released in an active form from a composition obtained by precipitating an active protein drug at a pH below 4.

In view of the above, our method of preparing sustained release protein drug compositions, i.e., generating and precipitating the protein drug compositions at pH 3, is contrary to accepted wisdom in the art. Proceeding contrary to accepted wisdom in

the art is evidence of nonobviousness (MPEP, section 2145, part X, D.3, page 2161). We refer to the findings of *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986):

> PTO acted erroneously in determining that claimed process for sulfonating diphenol sulfone at its molten state would be obvious from prior art, since references all suggest that lower temperatures are preferable, and none suggests that reaction may be advantageously produced at molten state, and since data produced by the inventor, and not challenged by PTO, show significant advantages of claimed invention, so that, on balance, inventor proceeded contrary to accepted wisdom, which is strong evidence of unobviousness (*In re Hedges*, 228 USPQ 685, part 1).

Thus, it would not have been obvious to prepare sustained release drug compositions containing protein drugs via precipitation at pH 3 because these operating conditions are contrary to the wisdom in the art, which teaches that active proteins can be denatured, and therefore rendered inactive, at this pH. We therefore assert that claims 12 (as amended)-26 are not rendered obvious by Suzuki and Igari on the grounds delineated in *In re Hedges*.

We respectfully request your consideration of the above discussion with regard to the rejection of the pending claims under 35 U.S.C. 103(a). As the next response due date falls on June 8, 2003, we would like to expedite the prosecution by inviting your supervisor to this interview. If you agree, please provide a copy of this letter to your supervisor before the interview. I thank you and look forward to hearing from you.

Very truly yours,

John T. Kendall, Ph.D.
Registration No. 50,680

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